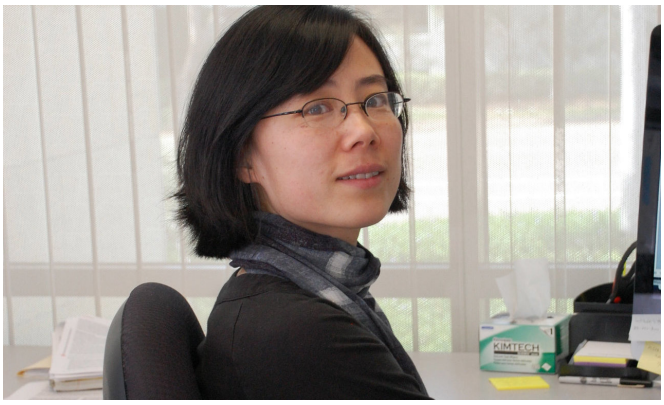
Discovery may advance neural stem cell treatments for brain disorders

24 January 2018



Crystal Zhao, Ph.D. Credit: Sanford Burnham Prebys Medical Discovery Institute

New research from Sanford Burnham Prebys Medical Discovery Institute (SBP) is among the first to describe how an mRNA modification impacts the life of neural stem cells (NSCs). The study, published in *Nature Neuroscience*, reveals a novel gene regulatory system that may advance stem cell therapies and gene-targeting treatments for neurological diseases such as Alzheimer's disease, Parkinson's disease, and mental health disorders that affect cognitive abilities.

"Being able to maintain viable stem cells in the brain could lead to regenerative therapies to treat injury and disease," says Jing Crystal Zhao, Ph.D., assistant professor at SBP. "Our study reveals a previously unknown but essential function of an mRNA modification in regulating NSC self-renewal. As NSCs are increasingly explored as a cell replacement therapy for neurological disorders, understanding the basic biology of NSCs—including how they self-renew—is essential to harnessing control of their in vivo functions in the brain."

NSCs are progenitor cells present not only during embryonic development but also in the adult brain. NSCs undergo a self-renewal process to maintain their population, as well as differentiate to give rise to all neural cell types: neurons, astrocytes and oligodedrocytes.

The current study focused on the self-renewal aspect of NSCs. Using knockout mice (KO) for the enzyme that catalyzes the m6A modification, Zhao's team found that m6A modification maintains NSC pool by promoting proliferation and preventing premature differentiation of NSCs. Importantly, the researchers found that m6A modification regulates this by regulating histone modifications.

Histones—the proteins in cells that bind and package DNA—and their modifications play an important role in whether genes are turned "on" or "off". Some histone modifications compact the DNA to hide a gene from the cell's protein-making machinery and consequently turn gene "off". On the other hand, histone modifications can also loosen up DNA for gene exposure to turn gene "on".

"Our findings are the first to illustrate cross-talk between mRNA and histone modifications, and may lead to new ways to target genes in the brain," says Zhao.

"Conceptually, we could use the modification, which is the methylation of adenosine residues, as a 'code' in mRNA to target histone modifications to turn gene on or off," says Zhao.

Drugs that alter histones have a long history of use in psychiatry and neurology, and increasingly in cancer. But current drugs that modify histones are often times non-specific; they work across the entire genome.

"Our current study addressed the interaction between mRNA and histone modification in a genome-wide scale. In the future, we plan to study such interaction on a gene-by-gene basis. Ultimately, by modulating mRNA modification and

its interacting histone modifications at a specific genomic region, we hope to correct aberrant gene expression in brain disorders with precision," explains Zhao.

More information: Yang Wang et al, N6-methyladenosine RNA modification regulates embryonic neural stem cell self-renewal through histone modifications, *Nature Neuroscience* (2018). DOI: 10.1038/s41593-017-0057-1

Provided by Sanford-Burnham Prebys Medical Discovery Institute